Fabry's disease: a form of chronic renal disease that may be diagnosed and treated

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INTRODUCTION

Fabry's disease is a hereditary disorder of the catabolism of glycosphingolipids produced by a deficit of lisosomal enzyme α-galactosidase A (α-GAL A), which leads to intracellular deposition, especially globotriaosylceramide (Gb3), within the vascular endothelium and other tissues. It is transmitted through the X chromosome and more than 400 mutations have been described so far (Human Gene Mutation Database, Institute of Medical Genetics, Cardiff http://archive.uwcm.ac.uk/uwcm/mg/hgmg0.html). Traditionally it has been considered recessively transmitted so that heterozygous women would be carriers and only 1% would develop the disease due to random inactivation of one of the X chromosomes (known as the Lyon's effect); however, there is more and more evidence that a great percentage of heterozygous women have partial enzymatic deficits and clinical manifestations with varying expression.[1-5]

It is a progressive disease that causes manifestations derived from dysfunction of the organ affected by the deposits, mainly the kidney, heart, nervous system, gastrointestinal tract, and the skin, although any organ or system of the body may be implicated.[4,6,7] Clinical[8,9] and experimental[10] studies have shown that Fabry's disease conditions a vascular inflammatory and pro-thrombotic state. In fact, the cardiovascular events, mainly ischemic heart disease[11] and cerebrovascular accidents,[12] are an important cause of morbimortality in these patients.

The diversity in the clinical presentation has been verified in recent years, with late partial presentation forms diagnosed by chance or through targeted studies, highlighting the fact that although it is a «rare» disease given its low frequency, the prevalence is higher than that initially thought, and thus there exists the suspicion that an undetermined number of affected families are not diagnosed. On the other hand, the availability of enzymatic replacement therapy (ERT) has opened new and encouraging expectations, of course accompanied by a certain level of confusion about the type and administration regimens of the two enzymes commercially available.

VARIANTS IN THE CLINICAL EXPRESSION

Fabry's disease manifests with high phenotypic variability, not only within a same mutation but also even within a same family.[13,14] In addition to environmental factors and maybe the participation of other genes, the severity or degree of involvement has been related with the residual activity of the α-GAL A enzyme. The classical form of the disease is usually characterized by a complete deficit of the enzymatic activity (less than 1%), with multisystemic implication, starting at childhood, reaching severe involvement by the third or fourth live decades[4,7,13,14] (table I). Partial enzymatic defects (1-30%) give rise to incomplete forms of late onset (from the age of 20-30 years), with predominantly heart and/or kidney involvement, and scarcity or absence of the

Table I. Clinical expression Fabry's disease. Classical form and heart and kidney variants

	Classical form	Heart	Kidney
Age a onset (years)	4-8	> 40	> 20
Severe involvement (age, years)	> 30	> 60	> 45
Angiokeratomas	Yes	–	–
Acroparesthesia	Yes	occasional	–
Hypo- or anhydrosis	Yes	–	ocasional
Corneal opacities/lenticonus	Yes	–	–
Gastrointestinal symptoms	Yes	–	–
Heart	LVH/CHD	LVH	LVH
Central nervous system	ACVA/TIA	–	–
Kidney	Proteinuria-CRD	Mild proteinuria	Proteinuria-IRC
Activated α-GAL	< 1%	1- 30%	1- 30%

LVH, Left ventricular hypertrophy; CHD, coronary heart disease; ACVA, acute cerebrovascular attack; TIA, transient ischemic atta ck; CRD, chronic renal disease.

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classical manifestations of the disease. In this sense, the «heart variant», in which left ventricular hypertrophy (LVH) would predominate,[15] and the «kidney variant» manifested by proteinuria and progressive renal failure often accompanied also by LVH[16-18] have been described (table I).

In the kidney there is deposition of Gb3 within the podocytes, mesangium, glomerular capillary endothelium, tubular epithelium, endothelial cells, the muscular layer of the arteries and arterioles, and in the interstitial cells.[19-21] The deposits progress and leads to glomerulosclerosis and interstitial fibrosis.[19,20] The initial data of renal involvement are isosthenuria, microalbuminuria and occasionally sings of proximal tubular dysfunction; later on proteinuria develops that in 20% of the cases may be higher than 3 g/24 h as well as renal failure, with or without arterial hypertension.[22] On the other hand, it has been reported that up to 10% of the patients with Fabry's disease have associated glomerular lesions for other reasons.[20]

The rate of progression of the nephropathy from the initial stages is not well known. In the classical form progression to severe end-stage chronic renal disease (CRD) (stage 5 of NKF-DOQI) is usual between the third an fifth decades of life,[22,23] whereas in the incomplete forms this may happen at advanced ages.[15,18] The progression of the renal involvement has been related to the stage of the enzymatic deficit.[22] Once renal failure is established, progression to a severe stage may be rapid, similar to diabetic nephropathy. In the series by Branton et al. a subgroup of 14 patients is described in whom progression of the renal function was known ending up in dialysis, having an average loss of glomerular filtration rate of -12 mL/min/1.73 m^2 per year, once the serum creatinine reached 1.5 mg/dL.[22] In another series of 447 patients (62% men), the mean time to double the serum creatinine value from a baseline value of 1.5 mg/dL was 39 months.[24]

EPIDEMIOLOGY AND DIAGNOSIS

It is estimated that the incidence of the classical form is 1 in 40,000-60,000 male liveborns (approximately 0.002%),[25] although the global incidence in both genders is unknown, which would include the late onset incomplete forms in both males and females. An Italian study on 37,104 male newborns has been published in which 12 (0.03%) were diagnosed with Fabry's disease, which was not previously known in the family and may correspond to late forms,[26] underscoring that the incomplete forms are more common that the classical form of the disease. In fact, prospective studies have shown that Fabry's disease is present in 3%-4% of the patients with LVH[15,27] and in 5% of a series of patients with acute cerebrovascular accidents of unknown etiology.[28]

The prevalence of Fabry's disease in patients with renal involvement is mainly based on the study of patients submitted to renal replacement therapy. While the European and American registries show a prevalence of 0.018% and 0.016%, respectively, (12% in both registries are women), studies done on dialysis patients have shown a much higher prevalence. When the activity of α-GAL A was used for initial screening by means of fluorescence in dry blood on a filter paper, the prevalence in male patients on dialysis with de novo diagnosis of Fabry's disease was 0.22-0.30%[31-33] (table II). The main problem with the dry drop method is the existence of false negative results,[34] especially in women.[35] By quantifying the enzymatic activity in whole blood, plasma and/or leukocytes, studies carried out in the USA, Europe and Japan yield a prevalence rate of the disease in male patients on dialysis of around 0.20%-1.2%[16,36-41] (table II). The three series published including female patients show a prevalence of 0%,[32] 0.05%, and 0.33%.[40] The mentioned data underscore that the prevalence of Fabry's disease in male patients on dialysis is 15-80 times higher than that expected according to the registries. These patients not diagnosed before the dialysis onset often present incomplete forms, with few or none extrarenal clinical manifestations of the disease but cardiac involvement, mainly LVH.[16,31]

The prevalence of Fabry's disease in CRD patients not submitted to renal replacement therapy is unknown. Undoubtedly, early diagnosis would be of

Table II. Prevalence studies of Fabry's disease in male patients on dialysis

	Country	Determination method of α-GALA	Number of diagnosed/ studied patients	Prevalence (%)
Spada, 2002[31]	Italy	Fluorescence of dry drop on paper	4/1,765	0.22
Kotanko, 2004[32]	Austria	Fluorescence of dry drop on paper	4/1,516	0.26
Merta, 2007[33]	Czech Republic	Fluorescence of dry drop on paper	4/1,338	0.30
Linthorst, 2003[36]	Holland	Enzymatic activity in whole blood	1/508	0.20
Walters, 2002[37]	USA	Enzymatic activity in plasma and leukocytes	9/1,903	0.47
Utsumi, 1999[38]	Japan	Enzymatic activity in plasma	2/440	0.45
Nakao, 2003[16]	Japan	Enzymatic activity in plasma and leukocytes	6/514	1.2
Ichinose, 2005[39]	Japan	Enzymatic activity in plasma	1/450	0.22
Tanaka, 2005[40]	Japan	Enzymatic activity in plasma and leukocytes	2/401	0.50
Bekri, 2005[41]	France	Enzymatic activity in leukocytes	1/106	0.94

great relevance for several reasons. On the one hand, because of the instauration of ERT, which may prevent or delay the disease progression, and on the other hand because it allows for performing a family study leading to early diagnosis and genetic counseling. In this sense, a multicenter study is being conducted in Spain targeting male patients with stages 1-5 CRD of unknown origin (not submitted to dialysis), in which the screening method is based on the measurement of plasma α-GAL A activity.[42] The preliminary results on 229 patients yield a prevalence of 0.9%. This represents two male patients aged 25 and 74 years, both with incomplete forms and with α-GAL A activity > 1% and absence of the classical clinical manifestations.

Thus, it is necessary to diagnose patients with Fabry's disease as early as possible. In the classical form, the multisystemic symptomatic complex may put on alert during childhood although more commonly the diagnosis is made in the second or third decades of life by means of renal biopsy and/or determination in the blood the α-GAL A activity, with confirmation by means of a genetic study. The incomplete forms arriving to the nephrology unit are more difficult to detect if programs are not established since, according to the experience in published studies, these patients cannot be biopsied given their characteristics.[16,31-33,36-41]

MANAGEMENT

The main goals in the management of Fabry's disease are symptoms relief, tissular damage reduction, and late complications prevention.[34,43-47] From the renal point of view, the actions will be focused on preventing renal disease or slowing its progression by means of the earliest intervention possible for which we count on ERT and general prevention measures for CRD.

From the year 2001, two recombinant human enzymes are available, alpha agalasidase produced from human fibroblasts (Replagal®, Shire Human Genetic Therapies, Inc), and beta agalasidase (Fabrazyme®, Genzyme Corp) produced from ovary cells of Chinese hamster. Phase I/II studies[48,49] led to marketing doses of alpha agalasidase of 0.2 mg/kg infused fortnightly, and 1 mg/kg of beta agalasidase also infused fortnightly at a similar cost of about 210.000 € per patient/year for an individual of 70 kg. Several clinical studies have evaluated the efficacy and safety of both formulations, and two trends with supporters of one or the other therapeutic strategies have emerged. Both products are able to reduce tissular deposition of Gb3,[50,51] and reduce LVH,[52,53] although the different inclusion criteria and study designs did not allow a direct comparison.

According to some information, it may be inferred that alpha agalasidase and beta agalasidase are similar, since they have the same specific activity per milligram of product administered, determined *in vitro* by Gb3 clearance in fibroblasts from the skin of patients with Fabry's disease,[54] and there is complete cross-reaction of IgG antibodies between these products.[55] Recently, Vedder et al. have published a single clinical comparative study which results also support the similarity between both formulations.[56] Alpha agalasidase and beta agalasidase were prospectively and randomly administered to 18 and 16 patients, respectively, at the same dose (0.2 mg/kg fortnightly), with a follow-up period of 24 months. No differences were observed between both treatments in the parameters studied: proteinuria, glomerular filtration (GF), LVH, neuropathic pain, plasma and urinary levels of Gb3, and occurrence of IgG antibodies.[56]

In 2001, two prospective controlled and randomized phase III studies with agalasidase alpha[50] and beta agalasidase[51] were published, and in both, phase IV extension studies were done, which allowed assessing the long-term renal function. Fifty-eight patients were included with beta agalasidase, 29 treated at standard doses (1 mg/kg/14 days) for 20 weeks, with the primary end-point of assessing the Gb3 deposits within the renal microvascular endothelium. A marked reduction in Gb3 deposits was observed at the kidney, skin, and heart.[51] With an extension to 11 months, in which all patients received ERT (the placebo group from week 20), it was verified that renal deposits were close to the null value.[57] These patients continued being assessed in two extension studies to 3[58] and 4.5 years.[59] The average values for proteinuria and GF remained with no significant changes although 6 patients experienced renal function deterioration. The main progression factors were proteinuria > 1 g/24 h and a percentage of glomerular sclerosis > 50% at baseline. It should be underscored that only 10 out of 58 patients had a GF rate < 90 mL/min/ 1.73 m^2 at the study beginning, of which 4 had renal function worsening and 6 remained in a stable situation.

The phase 3 study with alpha agalasidase included 26 patients, 14 treated at a dose of 0.2 mg/kg fortnightly for 24 weeks,[50] which was followed by a phase 4 study for 4.5 years, in which all patients received ERT from the sixth month and on.[61] The treatment did not change proteinuria, and the average GF rate significantly decreased at the end of the study period.[60] However, this decrease essentially occurred at the expense of the loss of renal function in all patients presenting stage 3 CRD at baseline, and some patients at stage 2.

Other observational studies highlight that ERT may stabilize the renal function in patients with stage 2 CRD, although it does not prevent progression in stage 3 CRD or less.[61,62] In the larger series with 201 men and women treated with alpha agalasidase it was observed that in a subgroup of 12 patients with stage 2 CRD the mean GF rate had decreased from 83.7 to 71.9 mL/min/1.73 m^2 in the year before starting with ERT, which was unchanged one year after from the ERT onset.[61] In the subgroup of 8 patients with stage 3 CRD, the ERT did not modify the renal failure progression rate.[61] One interesting study recently published showed how 11 male patients with the classical form of Fabry's disease and presenting renal function loss > -5 mL/min/1.73 m^2/year experienced a slowing in their progression when switched from a conventional regimen (0.2 mg/kg fortnightly) to a weekly regimen of 0.2 mg/kg (from -8.0 to -3.3 mL/min/1.73 m^2 per year, $p < 0.01$).[63] It is unclear whether this beneficial effect was due to the increase in the frequency of administration or the dose increase, or both. In any case, these results would apparently be in contradiction with the observation that

nor the dose not the frequency of administration had an influence on the magnitude of reduction in plasma Gb3 in a randomized study evaluating 18 patients with 5 different administration regimens of alpha agalasidase (0.1, 0.2, or 0.4 mg/kg/week, or 0.2 mg/kg fortnightly, or 0.4 mg/kg fortnightly).[64] It is likely that the Gb3 levels may not be a marker of severity and response to treatment in Fabry's disease, and the authors themselves underline that new studies are required to determine the best treatment regimen to achieve the best clinical outcomes.[64]

The renal, cardiac and cerebrovascular effects of ERT have been assessed in patients with established chronic renal failure in a prospective, randomized, and controlled study in which 51 patients were treated with beta agalasidase and 31 received placebo, with a mean GF rate of 53 and 52.4 mL/min/1.73 m2, respectively, and a median follow-up time of 18.5 months.[65] The average values of GF rate and proteinuria were not significantly different between both groups at the end of the study period. However, the group of treated patients presented a reduction in the risk of occurrence of renal (defined as an increase in creatinine values > 33%, dialysis or transplantation), cardiac and/or cerebrovascular events as compared with the control group. These beneficial effects were more evident in those patients with lower levels of proteinuria (< 1 g/24 h) and lesser renal function impairment (GF rate > 55 mL/min/1.73 m^2), inferring that both proteinuria and renal function may be considered as markers of the risk for cardiovascular complications and response to ERT in Fabry's disease. The importance of early implementation of ERT on both renal function progression and prevention of extrarenal complications has been underscored by Breunig et al. in a prospective study including 23 patients treated with beta agalasidase.[66] It was observed that in those patients with GF rate > 90 mL/min/1.73 m^2 the renal function remained stable and did not present clinical events, whereas in those having stage 2-4 CRD there was progression of renal failure and ERT did not prevent the occurrence of cardiac and cerebrovascular complications.[66]

About the immune response against the two enzymes, and taking as a reference the phase III studies with their extensions,[59,60] 90% of the patients treated with beta agalasidase developed IgG antibodies[59] *versus* 56% with alpha agalasidase.[60] These differences may be due to the different dose regimen and/or the method used, and not so much to the difference between both preparations since there is complete cross-reaction between both;[55] moreover, in a comparative study with equal dosing, the rate of sero-conversion was similar.[56] However, there was a decrease in antibody titers with both formulations, which reached undetectable levels in some patients. The importance of the occurrence and maintenance of IgG antibodies in treatment efficacy is unclear. In both studies[59,60] it is reported that sero-conversion has no influence on either Gb3 clearance within the renal tissue[59] or urinary clearance of Gb3 and progression of the GF rate.[60] Notwithstanding, other authors find that patients developing IgG antibodies had lower Gb3 urine clearance as compared with those without sero-conversion, for both alpha agalasidase and beta agalasidase,[56] which opens questions on these issues. About the adverse events, most of the patients treated with beta agalasidase and 56% of those treated with alpha agalasidase presented at least one episode during the follow-up. Most of these effects were mild, related with the infusion, and decreased with time.[59,60]

From these works it follows that in those patients with normal GF rate without proteinuria or with proteinuria < 1 g /24 hours, ERT prevents the progression of CRD and the occurrence of complications. In stage 2 CRD patients, the response to ERT is more difficult to predict, proteinuria > 1g/24 h being a factor indicating a worse prognosis. Already established glomerulosclerosis and interstitial damage prevent ERT from avoiding progression of CRD when GF rate is < 60 mL/min/1.73 m^2, although the treatment is justified by the possible prevention of complications and relieve of some of the symptoms.

It is generally observed that proteinuria is not reduced with ERT[50,51,56,59,60,66] in spite of the massive decrease in renal deposition of Gb3, even with normal GF rate.[50,51,66] This indicates the presence of already irreversible structural glomerular and interstitial lesions from the moment that proteinuria is present. However, enzymatic therapy may reduce microalbuminuria,[67] which is another reason for the need for early treatment. In any case, there is the idea that the general measures for every proteinuric nephropathy should be established in Fabry's disease with renal involvement, such as are diet, hypertension and hyperlipidemia management, and the use of angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor antagonists (ARA II).[68] The benefits from the proteinuria-reducing therapy with ACEI and/or ARA II have been showed in a recent work in which a decrease in proteinuria and renal function stabilization in stage 2 CRD patients treated with beta agalasidase was confirmed.[69]

Groups of experts have elaborated guidelines on the assessment and management of Fabry's disease.[70,71] One important issue is the recommendation on when ERT should be started. The Guidelines for the Study and Management of Fabry's disease (GSMFD) establish major and minor criteria so that to start on the therapy, 1 major criterion and 2 minor criteria would be needed; among them, proteinuria (> 300 mg/24 h in adults or > 5 mg/kg/day in children) and GF rate < 80 mL/min/1.73 m^2 are major criteria, whereas microalbuminuria falls within the minor criteria.[70] However, other guidelines recommend offering the enzymatic therapy to every adult (older than 16 years) male patient diagnosed with Fabry's disease independently of his stage of CRD, in children when symptoms occur, and in women if there are symptoms or signs of organic involvement.[71]

In dialysis patients, ERT would be indicated to prevent the extrarenal complications of the disease.[72] The administration of beta agalasidase during the hemodialysis session, of both high- and low-flow, is well tolerated without losing the enzymatic activity.[73] Although the typical lesions of Fabry's disease do not occur in the grafted kidney, ERT would also be justified to treat and prevent multisystemic involvement.[74]

KEY CONCEPTS

BASIC IDEAS ON FABRY'S DISEASE

1. Fabry's disease is a hereditary storage disease produced by a deficit in α-galactosidase A that leads to the accumulation of glycosphingolipids within the vascular endothelium and other tissues. It is transmitted linked to the X chromosome, and it is suffered by male patients and an unknown percentage of women with incomplete forms.

2. In the classical form there is multisystemic involvement, starting in childhood, and severe organic involvement by the third or fourth decades of life. Heart disease, cerebrovascular accidents, and particularly kidney disease condition the vital prognosis.

3. There are late-onset incomplete forms with partial enzymatic deficits and heart and kidney involvement, and the absence of other classical clinical manifestations.

4. The disease is more common than what is thought, and the prevalence in patients on renal replacement therapy is very much higher than that of official registries due to undiagnosed incomplete forms.

5. The progression to end-stage CRD may be prevented provided that enzymatic replacement therapy is started early.

6. Hence, the importance of following specific early detection programs that also lead to family study with the diagnosis of new cases.

CONCLUSIONS

To summarize, the prevalence of Fabry's disease is higher than that referred by official registries of patients on renal replacement therapy due to the existence of incomplete variants in the clinical expression of late onset, with a predominant involvement of the heart and the kidney and the absence of other typical manifestations. These incomplete forms are difficult to diagnose without the help of established programs. Given the importance of early diagnosis, these detection programs become paramount in the nephrology clinic. Proteinuria higher than 1g/24 h and/or the decrease in GF rate are prognostic factors, both for the occurrence of cardiac and cerebrovascular complications and for the response to ERT. ERT should be applied from early phases in order to prevent the occurrence of structural renal lesions, although some questions are still unanswered about the best treatment regimen regarding the dosing and frequency of administration. In patients with CRD, ERT may slow the progression at stages 1 and 2, and reduce the occurrence of cardiovascular complications at more advanced stages. Although the data available are scant, these patients would benefit from ACEI/ARA II therapy and other general measures preventing the progression of CRD.

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